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077369,686	06/21/89	DORSCHUG M.	ADOBE/30

ALLEN, M EXAMINER

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ART UNIT	PAPER NUMBER
1812	10

DATE MAILED: 07/07/92

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 4/21/92 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1, 6-13 are pending in the application.
   Of the above, claims 6-9 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1, 10-13 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev.9-89)

Claims 2-5 have been canceled. Claims 11-13 have been newly added. Claims 6-9 are withdrawn as being drawn to a non-elected invention. Claims 1 and 10-13 are currently under consideration by the examiner.

Applicant's arguments with respect to claims 1-10 have been considered but are deemed to be moot in view of the new grounds of rejection.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matt r developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1 and 11-13 are rejected under 35 U.S.C. § 103 as being unpatentable over either Markussen et al. (U.S. Patent No. 4,916,212) or Markussen et al. (EPO 163,529).

Both Markussen et al. references disclose the insulin variant B(1-29)-X_n-Y-A(1-21) produced recombinantly in yeast. "X" is a peptide chain with n amino acids, "n" is an integer from 0 to 33, and Y is Lys or Arg. X is preferably selected from the group consisting of Ala, Ser, and Thr. A preferred embodiment is B(1-29)-Ser-Lys-A(1-21). The precursor protein before cleavage would be a single peptide chain. This precursor is converted to human insulin by derivitization and treatment with trypsin. The serine is converted to Thr in this process. (See '212 at column 3, lines 36-46; Examples 11, 13, and 16; and claims.)

Claim 1 is drawn to a human insulin variant that is a single peptide chain of the formula B(1-30)-Arg-A(1-21). The amino acid at position 30 in human insulin is Thr.

As such, the differences between the specific embodiment of th prior art and applicant's composition the amino acid Ser instead of Thr at position 30 and Lys for Arg. The claimed generic formula of the prior art encompasses applicant's claimed

composition. The different amino acids selected by applicant for these positions are preferred embodiments in the prior art.

It would have been obvious to take the DNA sequence of Markussen et al. and encode Thr at amino acid position 30 and Arg instead of Lys. Both of these changes are conservative amino acid substitutions; both of these changes are to the amino acids found in human insulin; and both of these changes are pref rred choices disclosed by applicant. It would have been obvious to take the resulting DNA and express it in yeast to form the composition of claim 1. There would have been a high expectation of success based on successful recombinant production of the B(1-29)-Ser-Lys-A(1-21) variant in the prior art. The methods of preparation of mono-Arg insulin or insulin (claims 11-13) as recited would have been obvious over those taught by Markussen et al. It is noted that no method steps are recited in these claims.

Claim 10 is rejected under 35 U.S.C. § 103 as being unpatentable over Markussen et al. (EPO 163,529) or Markussen et al. (U.S. Patent No. 4,916,212) either in view of Goeddel et al. (EPO 055,945).

Both Markussen et al. references are applied as above.

Goeddel et al. teaches producing recombinant fusion proteins of insulin fused to another protein. The reference furth r teaches making a fusion protein with an insulin variant in which

the C chain of insulin contains only six amino acids. (See page 6, line 19 through page 8, line 2; abstract; claims; page 26-27.)

It would have been obvious to make the fusion proteins of Goeddel et al. using the insulin variant taught by either Markussen et al. reference. One would have been motivated by the known benefits of producing small peptides as fusion proteins in microorganism hosts and the success with another insulin variant in which the C chain is shortened.

Claims 10, 11, and 13 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited as described below. See M.P.E.P. §§ 706.03(n) and 706.03(z).

The specification discloses methods of preparing mono-Arg insulin, represented by formula II, from miniproinsulin, represented by formula I. However, this conversion cannot always be performed in a single vessel. The specification discloses a single reaction for the conversion of miniproinsulin produced in yeast to mono-Arg insulin (treating with trypsin). The specification discloses two separate reactions for the conversion of miniproinsulin produced in E. coli to mono-Arg insulin (denaturing with urea and renaturing which is followed by column purification, treatment of the eluted material with trypsin, see pages 14 and 15 of specification.). It is noted that formula I, B(1-30)-Arg-A(1-21), does not specify the positioning of the disulfide bonds in this single chain peptide as b ing positioned

as in insulin. Applicant has not enabled the breadth of the claims as the source of the miniproinsulin is not a limitation of the claims.

The specification enables an N-terminal fusion protein of IL-2 bonded via the linker Met-Ile-Glu-Gly-Arg to miniproinsulin. This fusion can be cleaved by cyanogen bromide. There is no evidence of record that IL-2 could be fused to the C-terminal of miniproinsulin. There is no description in the specification of a C-terminal fusion. Furthermore, there is no evidence in the prior art or of record that a C-terminal fusion to insulin, proinsulin, preproinsulin, or the A- or B-chains of insulin (when expressed individually) protects or stabilizes the insulin or precursor form from degradation in bacteria. It appears that all successful fusion proteins have been at the N-terminal.

Claims 11-13 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11-13 are indefinite for failing to recite any steps that comprise the method being claimed. The claims fail to recite the steps that convert miniproinsulin to mono-Arg insulin (claims 11 and 13) or insulin (claim 12). Claim 13 is drawn to the method of claim 11 "wherein all of the chemical reactions are carried out...". However, these chemical reactions lack

antecedent basis in claim 11, and furthermore, the intended chemical reactions are not specified in claim 13.

The Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1812.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4227.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne Porta Allen whose telephone number is (703) 308-0666.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

DAVID L. LACEY
SUPERVISORY PATENT EXAMINER
GROUP 180
7/6/92